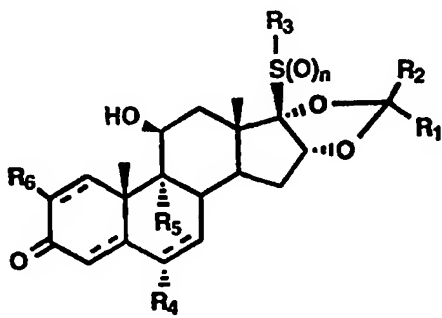




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<p>(21) International Application Number: PCT/GB93/02659 (22) International Filing Date: 24 December 1993 (24.12.93) (30) Priority Data: 9226917.4 24 December 1992 (24.12.92) GB 9303121.9 17 February 1993 (17.02.93) GB (71) Applicant (for all designated States except US): RHONE-POULENC RORER LIMITED [GB/GB]; RPR House, St Leonards Road, Eastbourne, East Sussex BN21 3YG (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): ASHTON, Michael, John [GB/GB]; Rhone-Poulenc Rorer Ltd., Dagenham, Essex RM10 7XS (GB). KARLSSON, Sven, Jan-Anders [SE/GB]; Rhone-Poulenc Rorer Ltd., Dagenham, Essex RM10 7XS (GB). VACHER, Bernard, Yvon, Jack [FR/GB]; Rhone-Poulenc Rorer Ltd., Dagenham, Essex RM10 7XS (GB). WITHNALL, Michael, Thomas [GB/GB]; Rhone-Poulenc Rorer Ltd., Dagenham, Essex RM10 7XS (GB). (74) Agents: BENTHAM, Stephen et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).</p>		<p>(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.</p>
<p>(54) Title: NEW STEROIDS</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>Steroids of formula (I) where — is independently at each of the 1,2-, 4,5- and 6,7-positions, a single or double bond; R₁ is a straight- or branched-chain C₁₋₄ alkyl or C₂₋₄ alkenyl; R₂ is hydrogen or methyl; R₃ is C₁₋₇ alkyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl or -CH₂R where R is halo, hydroxy, C₁₋₃ alkoxy or C₁₋₁₀ alkanoyloxy; R₄ is hydrogen, halo, hydroxy, keto or C₁₋₃ alkoxy when — at the 6,7-position forms a single bond, or hydrogen, halo or C₁₋₃ alkoxy when — at the 6,7-position forms a double bond; R₅ is hydrogen or halo; R₆ is hydrogen when — at the 1,2-position forms a single bond or hydrogen or chloro when — at the 1,2-position forms a double bond; and n is 0-2; and racemic mixtures and diastereoisomers thereof, processes for their preparation, pharmaceutical compositions containing them, and methods for their use, especially as antiinflammatories.</p>		

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"NEW STEROIDS"FIELD OF THE INVENTION

5

The present invention relates to novel antiinflammatory, immunosuppressive, and antiallergic compounds and to processes for their preparation. The invention also relates to pharmaceutical compositions containing the compounds. The invention also relates to the pharmacological
10 uses of the compounds.

15

More particularly, this invention relates to new therapeutically useful steroids, processes for their preparation, pharmaceutical compositions containing them, and methods for their use, especially as anti-inflammatories.

20

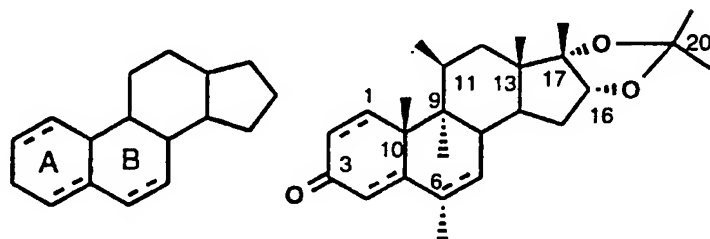
The object of the invention is to provide a steroid which possesses high antiinflammatory, immunosuppressive and antiallergic activity, or a pharmaceutical composition thereof, with high activity at the site of application, e.g. in the respiratory tract, on the skin, in the joints, in the intestinal tract, or in the eye, coupled with low glucocorticoid systemic potency.

25

A large number of natural and synthetic steroids are known, and many of them are useful in the treatment of human and animal subjects. Steroids which have antiinflammatory properties are known, but they suffer from the disadvantage that, after administration, they cause unwanted side-effects outside the organ or tissue which is desired to be treated. It is well known that, in the pharmaceutical field and, in particular, in the field of steroids, small differences in chemical structure can produce compounds with completely different pharmacological activities. The present invention provides
30 compounds which have never been described hitherto and which possess a

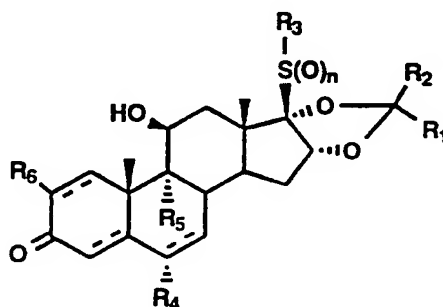
remarkable combination of very useful antiinflammatory activity with a very low ability to produce undesired side-effects.

The nomenclature used in this application is as follows:



The 1,2-position and 4,5-position of the A ring and 6,7-position of the B ring may be saturated or a double bond.

The compounds of this invention may be described by general formula I



formula I

where:

is independently at each of the 1,2-, 4,5- and 6,7-positions, a single or double bond;

R₁ is a straight- or branched-chain C₁₋₄ alkyl or C₂₋₄ alkenyl;

R₂ is hydrogen or methyl;

R₃ is C₁₋₇ alkyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl or -CH₂R where R is halo, hydroxy, C₁₋₅ alkoxy or C₁₋₁₀ alkanoyloxy;

R₄ is hydrogen, halo, hydroxy, keto or C₁₋₃ alkoxy when --- at the 6,7-position forms a single bond, or hydrogen, halo or C₁₋₃ alkoxy when

--- at the 6,7- position forms a double bond;

R₅ is hydrogen or halo;

5 R₆ is hydrogen when --- at the 1,2-position forms a single bond or hydrogen or chloro when --- at the 1,2-position forms a double bond; and

n is 0-2; and

racemic mixtures and diastereoisomers thereof.

10

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

The preferred compounds of this invention are described by formula I where:

15 --- is a double bond at the 1,2- and 4,5-positions and a single bond at the 6,7-position or a double bond at the 4,5- position and single bonds at the 1,2- and 6,7- positions.

The more preferred compounds are described by formula I

20 where:

--- is a double bond at the 4,5-position and single bonds at the 1,2- and 6,7-positions;

R₁ is alkyl;

R₂ is hydrogen, or methyl;

25 R₃ is alkyl, haloalkyl or heteroaryl;


R₄ is hydrogen, halo, or keto ;

R₅ is halo; .

R₆ is hydrogen; and

n is 0-2.

The most preferred compounds of this invention are described by formula I where:

5  is a double bond at the 4,5-position and single bonds at the 1,2-
and 6,7-positions;
R₁ is methyl, propyl or trans-prop-1-enyl ;
R₂ is hydrogen, or methyl;
R₃ methyl, fluoromethyl or pyridyl;
R₄ is hydrogen, fluoro, or keto ;
10 R₅ is fluoro;
R₆ is hydrogen; and
n is 0-2.

15 An embodiment of this invention is described where the 1,2-, 4,5- and 6,7- positions are all single bonds.

Compounds of formula I can exist in two diastereoisomeric forms because two different configurations are possible at the carbon atom in the 20 position. As a result, the invention includes the (20R)- and (20S)-diastereoisomers of the compounds of formula I, and mixtures thereof when R₁ and R₂ are different.

25 The preferred diastereoisomeric components are in the (20R)-configuration.

More specifically, the following compounds are within the scope of this invention:

30 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(methylthio)androst-1,4-dien-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-dien-3-one

5 (20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-dien-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(2-
pyridylthio)androsta-1,4-dien-3-one

10 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -
(methylsulphonyl)androsta-1,4-dien-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
15 (methylsulphiny)androst-1,4-dien-3-on

(20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylsulphiny)androst-1,4-dien-3-one

20 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -
(methylthio)androsta-1,4-dien-3-one

(20R,S)-16 α ,17 α -[(E)-2-butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-dien-3-one

25 (20R)-16 α ,17 α -[(E)-2-butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-dien-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
30 (isopropylthio)androsta-1,4-dien-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-17 β -ethylthio-9 α -fluoro-11 β -hydroxyandrosta-1,4-dien-3-one

5 (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(fluoromethylthio)androsta-1,4-dien-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-one

10 (20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-one

(20S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-one

15 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(2-pyridylthio)androsta-1,4-dien-3-one hydrate

(20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylsulphinyl)androsta-1,4-dien-3-one

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylsulphinyl)androsta-1,4-dien-3-one

25 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(fluoromethylthio)androsta-1,4-dien-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(fluoromethylthio)androst-4-en-3-one

30

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(fluoromethylthio)androst-4-en-3-one

5 (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(fluoromethylthio)androsta-1,4-dien-3-one

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(fluoromethylthio)androsta-1,4-dien-3-one

10 (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-dien-3-one

(20S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-dien-3-one

15 (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androst-4-en-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
20 (methylthio)androst-4-en-3-one

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androst-4-en-3-one

25 (20S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androst-4-en-3-one

(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-diene-3,6-dione

30

(20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-diene-3,6-dione

5 (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylsulphonyl)androsta-1,4-dien-3-one

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylsulphonyl)androsta-1,4-dien-3-one

10 (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androstan-3-one

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androstan-3-one

15 (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androst-4-ene-3,6-dione

(20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
20 (methylthio)androst-4-ene-3,6-dione

The compounds of this invention are extremely valuable in the local
treatment of inflammatory, allergic and immunological diseases. These
treatments include those currently treated by known steroids, such as diseases
25 of the respiratory system, e.g. asthma and rhinitis, diseases of the skin, e.g.
eczema, and diseases of the gastrointestinal tract, e.g. inflammatory bowel
disease. However, because of the advantage of having little or no side effects,
the compounds of this invention are much more desirable than previously
known compounds.

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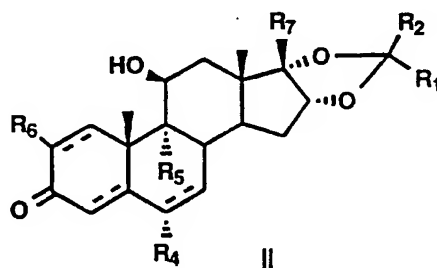
The use of the compounds of formula I, and of pharmaceutical formulations containing them in the treatment of such diseases, form features of the present invention.

5 These utilities have been demonstrated in pharmacological tests which are believed to correlate well to activity in humans and other mammals.

 The compounds of formula I can be prepared by the application or adaptation of known methods, by which is meant methods used hitherto or
10 described in the literature.

 The compounds of this invention may be prepared, for example, by the following reactions:

15 According to the present invention, compounds of formula I wherein n represents zero and --- , R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are as hereinbefore defined, are prepared by a radical fragmentation reaction from compounds of formula II,



20

wherein --- , R_1 , R_2 , R_4 , R_5 and R_6 are as hereinbefore defined, and R_7 represents a suitable group such as a 2-thioxo-1,2-dihydropyrid-1-ylloxycarbonyl group, by irradiation in the presence of a compound of the general formula:-

25



wherein R_3 is as hereinbefore defined, R_8 represents a hydrogen atom or an alkyl group containing up to about 7 carbon atoms, and m represents 0 or 2, under an inert atmosphere.

According to a further feature of the present invention, compounds of formula I wherein R_3 represents a pyridyl group, n represents zero, and --- , R_1 , R_2 , R_4 , R_5 and R_6 are as hereinbefore defined, are prepared by a similar radical fragmentation reaction from compounds of formula II, hereinbefore depicted, wherein --- , R_1 , R_2 , R_4 , R_5 and R_6 are as hereinbefore defined, and R_7 represents a 2-thioxo-1,2-dihydropyrid-1-yloxycarbonyl group, by irradiation in the absence of the said compounds of the general formula:-



According to a further feature of the invention, compounds of formula I can be prepared by the interconversion of other compounds of formula I.

For example, compounds of formula I wherein --- , R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are as hereinbefore defined and n represents 1 or 2 are prepared by the oxidation of compounds of formula I wherein --- , R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are as hereinbefore defined and n is less than in the desired product.

The oxidation may be performed by using a conventional oxidising agent such as potassium peroxymonosulphate to prepare products wherein n is 1 or a peracid to prepare products wherein n is 2.

As another example, compounds of formula I wherein --- , R_1 , R_2 , R_4 , R_5 and R_6 are as hereinbefore defined, n represents zero, and R_3 represents a halomethyl group are prepared by the halogenation of compounds of formula I wherein --- , R_1 , R_2 , R_4 , R_5 and R_6 are as hereinbefore defined, n represents zero, and R_3 represents a methyl group. For example, when R_3 represents a fluoromethyl group the reaction can be carried out by the action of xenon

difluoride, preferably in the presence of an activated molecular sieve and a non-nucleophilic base.

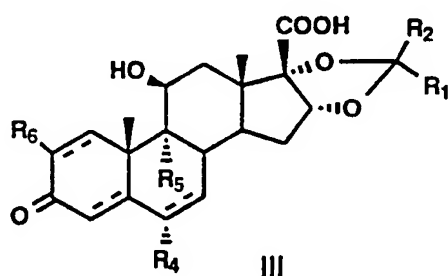
As another example, compounds of formula I wherein --- , n, R₁,
5 R₂, R₃, R₅ and R₆ are as hereinbefore defined, and R₄ represents an alkoxy group are prepared by the alkylation of compounds of formula I wherein --- , n, R₁, R₂, R₃, R₅ and R₆ are as hereinbefore defined, and R₄ represents a hydroxy group, by known methods, for example by reaction with a base followed by reaction with an alkyl halide, e.g. methyl
10 iodide when R₄ is methoxy.

As another example, compounds of formula I wherein one or more of the symbols --- , forms a single bond, the symbols otherwise being as hereinbefore defined, are prepared from compounds of formula I wherein
15 said symbol or symbols --- , form double bonds by hydrogenation in the presence of a catalyst. For example compounds of formula I wherein the symbol --- , forms a single bond in the 1,2-position, the symbols otherwise being as hereinbefore defined, are prepared from compounds of formula I wherein said symbol --- , forms a double bond by
20 hydrogenation in the presence of a rhodium compound, e.g. rhodium bis(triphenylphosphine) chloride.

The diastereoisomers of general formula I can be separated from their mixtures, by the application or adaptation of known methods, for example
25 chromatographic and recrystallisation techniques, or they may be separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

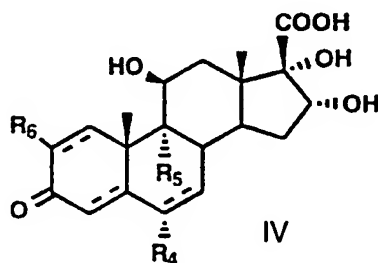
The starting materials and intermediates can be prepared by the application or adaptation of known methods, for example methods described in the Reference Examples or their obvious chemical equivalents.

- 5 For example, compounds of formula II can be prepared from compounds of formula III,



- 10 wherein --- , R_1 , R_2 , R_4 , R_5 and R_6 are as hereinbefore defined, by conversion of the carboxy group to the said group R_7 , by the application or adaptation of known methods.

- 15 Compounds of formula III can be prepared from compounds of the general formula IV,



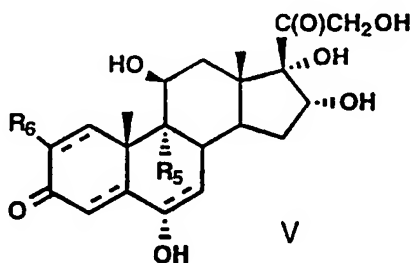
- 20 wherein --- , R_4 , R_5 and R_6 are as hereinbefore defined, by reaction with compounds of the general formula:-



wherein R_1 and R_2 are as hereinbefore defined and R_9 is a methyl or ethyl group, in the presence of a protic acid, e.g. perchloric acid.

5

Compounds of formula IV wherein R_4 represents a hydroxy group and --- , R_5 and R_6 are as hereinbefore defined, can be prepared from compounds of the general formula V,

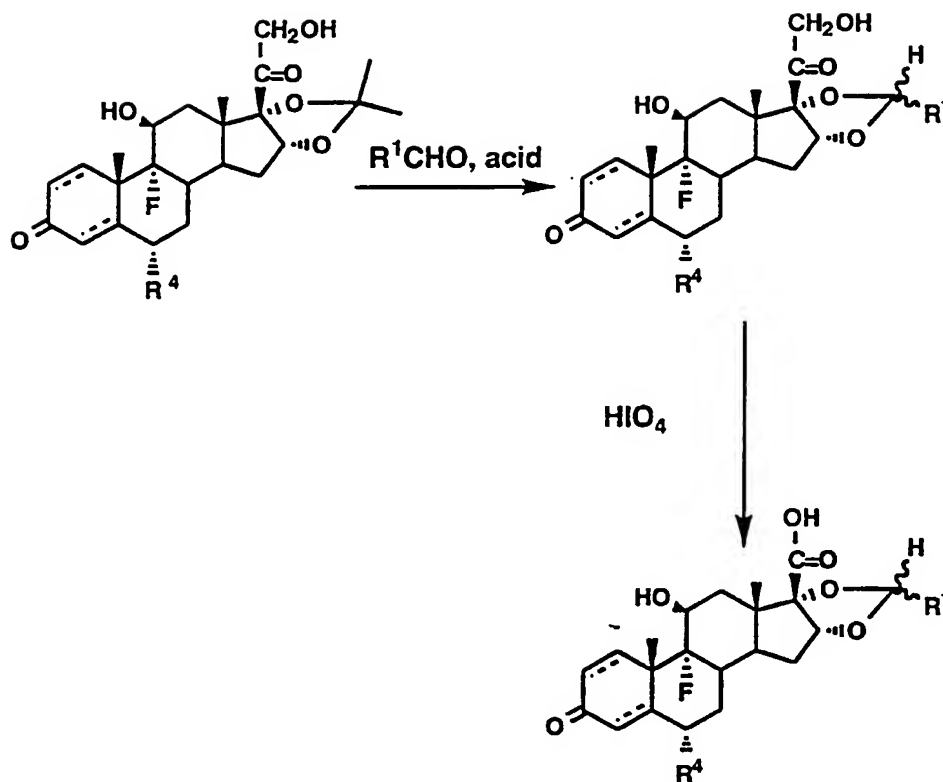


10

wherein --- , R_5 and R_6 are as hereinbefore defined, by reaction with potassium superoxide in the presence of an agent such as 1,4,7,10,13,16-hexaoxa-cyclooctadecane, preferably in a solvent such as dimethylformamide.

15

Alternatively, compounds of formula III can be prepared by the following reaction sequence.



Methods of Preparation

- 5 The following Examples illustrate the preparation of compounds according to the present invention. All 1H -NMR spectra are recorded at 400MHz. The chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviation in the text have the following significances: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, c = unresolved complex peak, b = broad signal.
- 10 Optical rotations are measured using a polarimeter model AA-10.

Example 1

1.1) 9 α -Fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(methylthio)androsta-1,4-dien-3-one

5 A solution of 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(2-thiopyridone-1-oxycarbonyl)androsta-1,4-dien-3-one (2.1 g) in dimethyl disulfide (80 ml) is irradiated with a tungsten lamp (300 W) at -8°C under an atmosphere of nitrogen until the reaction is complete (1-3 hours). The dimethyl

10 disulfide is removed under vacuo and the residue purified by low pressure liquid chromatography on silica gel eluting with chloroform. The solid obtained after evaporation of the solvent is recrystallised from ethyl acetate to give 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(methylthio)androsta-1,4-dien-3-one as a white solid (0.5 g, 1.2 mmol), m.p. 256°C; [N.M.R. (DMSO, d₆): 1.13

15 (s, 3H), 1.27-1.39 (m, 1H), 1.33 (s, 3H), 1.44 (dd, 1H), 1.50 (s, 3H), 1.54 (s, 3H), 1.59 (dt, 1H), 1.68 (d, 1H), 1.81 (c, 1H), 1.93-2.03 (m, 2H), 2.11 (s, 3H), 2.35 (dt, 1H), 2.4 (m, 1H), 2.63 (dt, 1H), 4.13 (c, 1H), 4.39 (d, 1H), 5.34 (c, 1H), 6.01 (s 1H), 6.23 (dd, 1H), 7.28 (d, 1H);

Found: C, 65.3; H, 7.5%
 20 Calculated for C₂₃H₃₁FO₄S: C, 65.4; H, 7.4%].

1.2) (20R)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-one

25 (20S)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-one

A solution of 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-3-oxo-6 α ,9 α -difluoro-11 β -hydroxy-6 α ,17 α -butylidenedioxyandrosta-1,4-diene-17 β -carboxylate (2g) in

30 dimethyl formamide (5 ml) and dimethyl disulfide (75 ml) is treated as described above. After work up, the powder obtained is recrystallised from ethyl acetate to

give (20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-one (0.63 g, 1.44 mmol) as a white solid in a stereoisomeric purity greater than 98%, m.p. 187 $^{\circ}$ C; [N.M.R. (DMSO, d₆): 0.87 (t, 3H), 1.18 (s, 3H), 1.23-1.61 (m, 7H), 1.50 (s, 3H), 1.61 (d, 1H), 1.80 (m, 1H),
 5 1.93-2.05 (m, 2H), 2.09 (s, 3H), 2.33 (dd, 1H), 2.4 (m, 1H), 2.64 (dt, 1H), 4.12 (c, 1H), 4.14 (d, 1H), 5.13 (t, 1H), 5.35 (c, 1H), 6.02 (s, 1H), 6.23 (dd, 1H), 7.28 (d, 1H);

Found: C, 63.4; H, 7.3%

Calculated for C₂₄H₃₂F₂O₄S: C, 63.4; H, 7.1%].

10 and (20S)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -methylthioandrosta-1,4-dien-3-one is obtained as a white solid (0.6 g), m.p. 198-9 $^{\circ}$ C; [N.M.R. (DMSO, d₆): 0.87 (t, 3H), 1.08 (s, 3H), 1.3-1.4 (m, 3H), 1.49 (s, 3H), 1.5-1.65 (m, 3H), 1.59 (d, 1H), 1.75-1.9 (m, 2H), 1.95 (dt, 1H), 2.05 (s, 3H), 2.25 (c, 1H), 2.4-2.51 (m, 1H), 4.1-4.2 (c, 1H), 4.78 (d, 1H), 5.11
 15 (t, 1H), 5.44 (c, 1H), 5.63 (m, 1H), 6.1 (s, 1H), 6.28 (dd, 1H), 7.25 (dd, 1H);
 Found: C, 63.9; H, 7.2%
 Calculated for C₂₄H₃₂F₂O₄S: C, 63.4; H, 7.1%]

1.3) (20R)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-
 20 17 β -(methylthio)androsta-1,4-dien-3-one

2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-3-oxo-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxyandrosta-1,4-diene-17 β -carboxylate (19.5 g) is dissolved in dichloromethane (40 ml) and dimethyl disulfide (430 ml) is
 25 irradiated as described above. The reaction mixture is concentrated in vacuo, the residue is taken up in ethyl acetate (400 ml) and washed successively with hydrochloric acid (1 N, two times 200 ml), water (200 ml) and brine (two times 200 ml). The ethyl acetate phase is dried over sodium sulfate, filtration of the dessicant and concentration in vacuo give a pale yellow foam (13.1 g) from
 30 which the mixture of epimers (20R,S)-in proportion of 80% to 20% is resolved by

preparative HPLC using a Dynamax RP-18 column and methanol/water as mobile phase. (20R)-16 α ,17 α -butylenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(methylthio)-androsta-1,4-dien-3-one(is obtained as a white solid (6.55 g, 14.4 mmol), m.p. 204-6 $^{\circ}$ C; $[\alpha]^{26} = +108^{\circ}$, $c = 0.067$ (CH₃CN); [N.M.R. (DMSO, d6):

5 0.87 (t, 3H), 1.16 (s, 3H), 1.33-1.43 (m, 3H), 1.43-1.54 (m, 1H), 1.50 (s, 3H), 1.54-1.63 (m, 3H), 1.73 (d, 1H), 1.97-2.08 (m, 2H), 2.10 (s, 3H), 2.26 (c, 1H), 2.48-2.63 (m, 1H), 4.14 (c, 1H), 4.16 (d, 1H), 5.12 (t, 1H), 5.43 (c, 1H), 5.63 (m, 1H), 6.11 (s, 1H), 6.30 (dd, 1H), 7.26 (dd, 1H);

Found: C, 65.8; H, 7.6%

10 Calculated for C₂₄H₃₃FO₄S: C, 66.0 H, 7.6%].

1.4) (20R)-16 α ,17 α -[(E)-2-Butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-one

15 In an analogous manner 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-3-oxo-9 α -fluoro-11 β -hydroxy-16 α ,17 α -(E)-but-2-enylidenedioxyandrosta-1,4-diene-17 β -carboxylate (1.85 g) as starting material gives after recrystallisation in diethyl ether (20R)-16 α ,17 β -[(E)-2-butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-one as a white solid (0.25 g, 0.57 mmol) in a

20 stereoisomeric purity greater than 96%, m.p. 204-6 $^{\circ}$ C; [N.M.R. (DMSO, d6): 1.17 (s, 3H), 1.33 (m, 1H), 1.44 (dd, 1H), 1.50 (s, 3H), 1.57 (dt, 1H), 1.69 (dd, 3H), 1.71 (d, 1H), 1.80 (m, 1H), 1.92-2.04 (m, 2H), 2.10 (s, 3H), 2.33 (dd, 1H), 2.30-2.50 (m, 1H), 2.63 (dt, 1H), 4.11 (c, 1H), 4.18 (d, 1H), 5.35 (c, 1H), 5.37-5.45 (m, 2H), 5.96 (m, 1H), 6.02 (s, 1H), 6.24 (dd, 1H), 7.28 (d, 1H);

25 Found: C, 66.5; H, 7.30%

Calculated for C₂₄H₃₁FO₄S: C, 66.33; H, 7.19%].

1.5) 6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(methylthio)androsta-1,4-dien-3-one

- In an analogous manner 2-thioxo-1,2-dihydropyrid-1-yl 3-oxo-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxyandrosta-1,4-diene-17 β -carboxylate (2.5 g) gives after purification by low pressure liquid chromatography on silica gel eluting with a mixture of dichloromethane (95%) and methanol (5%) followed by recrystallisation of the white solid obtained from acetonitrile 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(methylthio)androsta-1,4-dien-3-one (0.46 g, 1.0 mmol), m.p. 255-6^oC; [N.M.R. (DMSO, d₆): 1.13 (s, 3H), 1.33 (s, 3H), 1.45 (m, 2H), 1.50 (s, 3H), 1.55 (s, 3H), 1.64 (dd, 1H), 1.70 (d, 1H), 1.96-2.09 (m, 2H), 2.12 (s, 3H), 2.26 (m, 1H), 2.45-2.62 (m, 1H), 4.13 (c, 1H), 4.42 (d, 1H), 5.41 (c, 1H), 5.63 (m, 1H), 6.10 (s, 1H), 6.29 (dd, 1H), 7.25 (dd, 1H);
- Found: C, 62.6; H, 6.92%
Calculated for C₂₃H₃₀F₂O₄S: C, 62.71; H, 6.86%].

Example 2

2.1) (20R,S)-16 α ,17 α -Butylidenedioxy-17 β -ethylthio-9 α -fluoro-11 β -hydroxyandrosta-1,4-dien-3-one

- 2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-3-oxo-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxyandrosta-1,4-diene-17 β -carboxylate (1 g) dissolved in dimethyl formamide (5 ml) and diethyl disulfide (35 ml) is irradiated at -40^oC for 3 hours under a nitrogen atmosphere. The solvents are removed in vacuo (70^oC, 0.4 mmHg) and the residue purified by low pressure liquid chromatography on silica gel eluting with chloroform. The solid obtained after evaporation of the solvent is recrystallised from a mixture of ethyl acetate and hexane to give (20R,S)-16 α ,17 α -butylidenedioxy-17 β -ethylthio-9 α -fluoro-11 β -

hydroxyandrosta-1,4-dien-3-one as a white solid (0.30 g, 0.66 mmol) in an epimeric proportion of 85/15%, m.p. 228-9°C; [N.M.R. (DMSO, d6): 0.87 (t, 2.55H), 0.89 (t, 0.45H), 1.07 (s, 0.45H), 1.17 (m, 5.55H), 1.27-1.46 (m, 4H), 1.49 (s, 0.45H), 1.50 (s, 2.55H), 1.50-1.60 (m, 3H), 1.73 (d, 1H), 1.80 (m, 1H), 1.95 (dt, 1H), 2.02 (dt, 1H), 2.33 (dd, 1H), 2.33-2.47 (m, 1H), 2.64 (dt, 1H), 2.68 (q, 2H), 4.11 (d, 0.85H), 4.13 (c, 1H), 4.75 (d, 0.15H), 5.07 (t, 0.15H), 5.16 (t, 0.85H), 5.33 (c, 0.85H), 5.38 (c, 0.15H), 6.0 (s, 1H), 6.22 (dd, 1H), 7.28 (d, 1H); Found: C, 66.3; H, 7.90% Calculated for C₂₅H₃₅FO₄S: C, 66.6; H, 7.80%].

2.2) (20R,S)-16 α ,17 α -Butyridenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(isopropylthio)androsta-1,4-dien-3-one

2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-3-oxo-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butyridenedioxyandrosta-1,4-diene-17 β -carboxylate (2.40 g) dissolved in dimethyl formamide (10 ml) and diisopropyl disulfide (40 ml) is treated as described above. Recrystallisation from a mixture of ethyl acetate and petroleum spirit gives (20R,S)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butyridenedioxy-17 β -isopropylthio-androsta-1,4-dien-3-one as a white solid (0.60 g, 1.29 mmol) in an epimeric proportion of 85/15%, m.p. 235°C; [N.M.R. (DMSO, d6): 0.88 (t, 2.55H), 0.92 (t, 0.45H), 1.05 (s, 0.45H), 1.17 (s, 2.55H), 1.23 (d, 3H), 1.28 (d, 3H), 1.30-1.45 (m, 4H), 1.49 (s, 0.45H), 1.50 (s, 2.55H), 1.50-1.63 (m, 3H), 1.67-1.84 (m, 2H), 1.95 (dt, 1H), 2.07 (dt, 1H), 2.32 (dd, 1H), 2.35-2.50 (m 1H), 2.63 (dt, 1H), 3.42 (m, 1H), 4.08 (d, 0.85H), 4.15 (c, 1H), 4.73 (d, 0.15H), 5.08 (t, 0.15H), 5.16 (t, 0.85H), 5.37 (c, 1H), 6.02 (s, 1H), 6.23 (dd, 1H), 7.28 (d, 1H); Found: C, 66.6; H, 8.10% Calculated for C₂₆H₃₇FO₄S: C, 67.2; H, 8.00%].

Example 3

3.1) 6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(fluoromethylthio)androsta-1,4-dien-3-one

5 A mixture of 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -methylthio-androsta-1,4-dien-3-one (5.06 g, 11.5 mmol), 2,6-di-*t*-butyl-4-methylpyridine (5.19 g, 25.3 mmol) and activated molecular sieve (type 4 A, 7.5 g) in dry dichloromethane (250 ml) is stirred for
10 1.5 hours under an argon atmosphere at 20°C. Xenon difluoride (2.15 g, 12.7 mmol) is added in one portion and the mixture stirred at 20°C for 3 hours. After the molecular sieve is filtered off, the homogeneous solution is poured into ice cold water (500 ml), decanted and the aqueous phase extracted with dichloromethane (200 ml). The combined organic phases are washed with brine
15 (100 ml) and concentrated in vacuo. The residue is taken up in ethyl acetate (500 ml), washed with hydrochloric acid (1 N, three times 250 ml), water (250 ml), brine (250 ml) and then the organic phase is dried over magnesium sulfate. Filtration of the desiccant and concentration in vacuo gives a white solid (3.6 g) which is purified by preparative HPLC using a Dynamax RP-18 column and
20 methanol/water as mobile phase. 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(fluoromethylthio)androsta-1,4-dien-3-one (2.4 g, 5.23 mmol) is obtained as a white solid which is recrystallised from acetonitrile, m.p. 268-9°C; $[\alpha]^{26} = +162^\circ$, $c = 0.057$ (CH₃CN); [N.M.R. (DMSO, d₆): 1.06 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.46-1.57 (m, 2H), 1.50 (s, 3H), 1.69 (dt, 1H), 1.73 (d, 1H), 1.82 (dt, 1H), 2.05 (dt, 1H), 2.29 (c, 1H), 2.47-2.63 (m, 1H), 4.15 (c, 1H),
25 4.63 (d, 1H), 5.52 (c, 1H), 5.62 (m, 1H), 5.65 (dd, 1H), 5.79 (dd, 1H), 6.10 (s, 1H), 6.29 (dd, 1H), 7.25 (dd, 1H);
Found: C, 60.2; H, 6.37%
Calculated for C₂₃H₂₉F₃O₄S: C, 60.25; H, 6.37%].

30

3.2) (20R)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-
17 β -(fluoromethylthio)androsta-1,4-dien-3-one

(20R)-9 α -Fluoro-11 β -hydroxy-16 α ,17 α -butyli-denedioxy-
 5 17 β -methylthio-androsta-1,4-dien-3-one (2.0 g, 4.58 mmol) is treated with
 2,6-di-*t*-butyl-4-methylpyridine (2.05 g, 10 mmol) and xenon difluoride (0.85 g,
 5.0 mmol) in dichloromethane (100 ml) as described above. After work up, the
 residue is purified by low pressure liquid chromatography on silica gel eluting
 with chloroform and the white solid obtained (0.6 g) recrystallised from a mixture
 10 of ethyl acetate and petroleum spirit to give (20R)-16 α ,17 α -butylidenedioxy-9 α -
 fluoro-11 β -hydroxy-17 β -(fluoromethylthio)androsta-1,4-dien-3-one (0.25 g, 0.55
 mmol), m.p. 160 $^{\circ}$ C (dec.); [N.M.R. (DMSO, d_6): 0.87 (t, 3H), 1.09 (s, 3H),
 1.26-1.41 (m, 3H), 1.44-1.50 (m, 1H), 1.50 (s, 3H), 1.54-1.64 (m, 3H), 1.73 (d,
 1H), 1.78-2.0 (m, 3H), 2.33 (dd, 1H), 2.35-2.50 (m, 1H), 2.62 (dt, 1H), 4.17 (c,
 15 1H), 4.38 (d, 1H), 5.09 (t, 1H), 5.45 (c, 1H), 5.59 (dd, 1H), 5.72 (dd, 1H), 6.01 (s,
 1H), 6.22 (dd, 1H), 7.28 (d, 1H);
 Found: C, 63.4; H, 7.10%
 Calculated for C₂₄H₃₂F₂O₄S: C, 63.4, H, 7.10%].

20 3.3) (20R)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -
hydroxy-17 β -(fluoromethylthio)androsta-1,4-dien-3-one

(20R)-6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -methylthio-
 androsta-1,4-dien-3-one (1.7 g, 3.5 mmol) is treated with
 25 2,6-di-*t*-butyl-4-methyl-pyridine (1.57 g, 7.66 mmol) and xenon difluoride (0.65 g,
 3.8 mmol) in dichloromethane (100 ml) as described above. After work up, the
 white powder obtained (1.3 g) is purified by low pressure liquid chromatography
 on silica gel eluting with chloroform to give (20R)-16 α ,17 α -butylidenedioxy-
 6 α ,9 α -difluoro-11 β -hydroxy-17 β -(fluoromethylthio)androsta-1,4-dien-3-one as a
 30 white solid (0.32 g, 0.68 mmol), m.p. 145-6 $^{\circ}$ C; [N.M.R. (DMSO, d_6): 0.88 (t,

3H), 1.08 (s, 3H), 1.31-1.50 (m, 3H), 1.50 (s, 3H), 1.50-1.55 (m, 1H), 1.53-1.68 (m, 3H), 1.75 (d, 1H), 1.89 (dt, 1H), 2.03 (dt, 1H), 2.27 (c, 1H), 2.50-2.66 (m, 1H), 4.17 (c, 1H), 4.40 (d, 1H), 5.09 (t, 1H), 5.53-5.10 (m, 1.5H), 5.58 (dd, 1H), 5.65-5.74 (m, 0.5H), 5.73 (dd, 1H), 6.11 (s, 1H), 6.30 (dd, 1H), 7.24 (dd, 1H);

5 Found: C, 61.2; H, 6.70%

Calculated for $C_{24}H_{31}F_3O_4S$: C, 60.99; H, 6.60%].

Example 4

10 4.1) (20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-
17 β -(2-pyridylthio)androsta-1,4-dien-3-one

2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-3-oxo-9 α -fluoro-11 β -hydroxy-
16 α ,17 α -butylidenedioxyandrosta-1,4-diene-17 β -carboxylate (0.60 g) dissolved
15 in dichloromethane (50 ml) is irradiated under a nitrogen atmosphere as
described above. The temperature is maintained at 20°C by external cooling
and irradiation continued until the reaction mixture became colourless (45
minutes). The reaction mixture is concentrated in vacuo and the product isolated
by low pressure liquid chromatography on silica gel eluting with chloroform.

20 Recrystallisation from a mixture of ethyl acetate and petroleum spirit gives
(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(2-pyridylthio)-
androsta-1,4-dien-3-one as a white solid (0.15 g, 0.30 mmol) in an epimeric
proportion of 85/15%, m.p. 215°C; N.M.R. (DMSO, d6): 0.75 (t, 0.45H), 0.88 (t,
2.55H), 1.17 (m, 1H), 1.20 (s, 3H), 1.22-1.45 (m, 3H), 1.46 (s, 3H), 1.45-1.55
25 (m, 2H), 1.56-1.69 (m, 2H), 1.82 (m, 2H), 1.94 (dt, 1H), 2.33 (dd, 1H), 2.40 (m,
1H), 2.62 (dt, 1H), 3.98 (c, 1H), 4.45 (d, 0.85H), 5.03 (d, 0.15H), 5.10 (t, 0.15H),
5.22 (t, 0.85H), 5.31 (c, 0.85H), 5.38 (c, 0.15H), 6.0 (s, 1H), 6.19 (dd, 0.85H),
6.21 (dd, 0.15H), 7.20 (d, 0.85H), 7.25 (d, 0.15H), 7.29 (dt, 1H), 7.66 (dd, 1H),
8.21 (dt, 1H), 8.48 (ddd, 1H);

30 Found: C, 67.0; H, 6.87; N, 2.70%

Calculated for $C_{28}H_{34}FNO_4S$: C, 67.30; H, 6.80; N, 2.80%].

4.2) 9 α -Fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(2-pyridylthio)androsta-1,4-dien-3-one

5

By proceeding in a similar manner 2-thioxo-1,2-dihydropyrid-1-yl 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (9g) gives after work up a white solid (2.9 g). Recrystallisation from diethyl ether gives 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(2-pyridylthio)androsta-1,4-dien-3-one hydrate as a yellow solid (0.63 g), m.p. 183-6°C; [N.M.R. (DMSO, d6): 1.14-1.22 (m, 4H), 1.25-1.42 (m, 1H), 1.38 (s, 3H), 1.47 (s, 3H), 1.47-1.55 (m, 1H), 1.59 (s, 3H), 1.62-1.75 (m, 1H), 1.78-1.92 (m, 2H), 1.93-2.05 (m, 1H), 2.29-2.48 (m, 2H), 2.55-2.67 (m, 1H), 3.98 (c, 1H), 4.69(d, 1H), 5.29 (c, 1H), 6.0 (s, 1H), 6.19 (dd, 1H), 7.2 (d, 1H), 7.24 (m, 1H), 7.67-7.75 (m, 2H), 8.45 (m, 1H); Found: C, 64.1; H, 6.49; N 2.50% Calculated for $C_{27}H_{32}FNO_4S \cdot H_2O$: C, 64.39; H, 6.40; N, 2.78%].

20 Example 5

5.1) (20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-diene-3,6-dione

25 Irradiation of 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-3,6-dioxo-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxyandrosta-1,4-diene-17 β -carboxylate (1.83g, 3.28mmol) in the presence of dimethyl disulfide according to the procedures described above gives a pale cream solid (1.36g) which is recrystallized from diethyl ether to give an off-white solid (1.1g) which is
30 recrystallized a second time from acetonitrile to afford (20R,S)-16 α ,17 α -

butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-diene-3,6-dione as a white solid (0.33g, 0.73mmol) in a diastereoisomeric purity greater than 95%, m.p. 241-243°C; [NMR(DMSO, d₆): 0.88(t, 3H), 1.19(s, 3H), 1.33-1.47(m, 3H), 1.49(s, 3H), 1.55-1.64(m, 3H), 1.82(d, 1H), 2.07(m, 2H), 2.10(s, 3H), 2.29(dd, 1H), 2.73(dd, 1H), 2.73-2.95(m, 1H), 4.17(d, 1H), 4.23(c, 1H), 5.13(t, 1H), 5.61(c, 1H), 6.29(d, 1H), 6.40(dd, 1H), 7.43(d, 1H); Found: C, 64.0; H, 7.00%. Calculated for C₂₄H₃₁F₀₅S: C, 64.0; H, 6.93%].

Example 6

6.1) (20R,S)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrost-4-ene-17 β -carboxylic acid

To a degassed (N₂) solution of methanol (250ml) and water (15ml) is added sodium hydroxide pellets (5.52g, 138mmol). When homogeneous, (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrost-1,4-diene-17 β -carboxylic acid (12.48g, 27.6mmol) is added in one portion and the suspension stirred until a yellow solution is obtained. The reaction mixture is treated dropwise at room temperature with iron pentacarbonyl (36.31ml, 276mmol), then heated at 50°C for 20 hours under an atmosphere of nitrogen. The cooled reaction mixture is poured into an ice-cold aqueous solution of sulfuric acid (4N, 1000ml), dichloromethane (750ml) is then added, and after decantation the clear aqueous layer is discarded. The organic phase washed with brine (500ml), dried over sodium sulfate, filtered and concentrated to half of the original volume by evaporation in vacuo. The resulting residue is filtered on a pad of silica gel, eluting first with dichloromethane, then with ethyl acetate, and finally with a mixture of ethyl acetate and methanol (1:1). Concentration in vacuo gives a white foam which is triturated with diisopropyl ether to give: (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrost-4-ene-17 β -carboxylic acid as an off-

white solid (12.7g, 27.7mmol), m.p. 210°C (dec.); [NMR(DMSO, d₆):
 0.87(t, 3H), 0.93(s, 2.7H), 0.96(s, 0.3H), 1.25-
 1.60(m, 6H), 1.49(s, 3H), 1.75(d, 2H), 1.91-2.0(m, 2H), 2.0-2.1(m, 1H), 2.16(c, 1H),
 2.22-2.37(m, 2H), 2.37-2.55(m, 2H), 4.15(c, 1H), 4.68(t, 0.9H), 4.89(c, 0.9H),
 5.10(d, 0.1H), 5.15(c, 1H), 5.21(t, 0.1H), 5.50(c, 1H), 5.70(s, 0.1H), 5.81(s, 0.9H)];

6.2) (20R,S)-16 α ,17 α -Butylenedioxy-6 α ,9 α -difluoro-
 11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic
 10 diethyl phosphoric anhydride

By proceeding as described in the Reference Examples, (20R,S)-
 16 α ,17 α -butylenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-
 17 β -carboxylic acid (12.6g, 27.7mmol) gives (20R,S)-16 α ,17 α -butylenedioxy-
 15 6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl
 phosphoric anhydride (17.2 g crude) which is used without further purification in
 the next step.

6.3) 2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -
 20 butylenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-
oxoandrosta-1,4-diene-17 β -carboxylate

By proceeding as described in the Reference Examples, (20R,S)-
 16 α ,17 α -butylenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-
 25 17 β -carboxylic diethyl phosphoric anhydride (17.2g) gives after work up 2-
 thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -butylenedioxy-6 α ,9 α -difluoro-
 11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (16.6g) which is used as
 such in the next step.

6.4) (20R,S)-6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,
17 α -butylidenedioxy-17 β -methylthioandrost-4-en-3-one

By proceeding as described in Example 1, 2-thioxo-1,2-dihydropyrid-1-yl
 5 (20R,S)-3-oxo-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxyandrost-4-
 ene-17 β -carboxylate (16.6g), as starting material affords after work up an off-
 white powder (12g) which is purified by low pressure liquid chromatography on
 silica gel, eluting with a mixture of diethyl ether and petroleum spirit (75:25).
 The white solid obtained (6g) is recrystallised from acetonitrile to give (20R,S)-
 10 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -methylthioandrost-4-
 en-3-one (4g) as a mixture of epimers (20R,S)-in proportions 90:10, which is
 resolved by preparative HPLC using a Dynamax RP-18 column and
 methanol/water as mobile phase. The (20R)-epimer is obtained as a white
 solid (3.4g, 7.45mmol), m.p. 180°C; [NMR(DMSO, d6):
 15 0.90(t, 3H), 1.15(s, 3H), 1.36-1.54(m, 7H), 1.49(s, 3H), 1.72(d, 1H), 1.93-2.10(m, 3H),
 2.09(s, 3H), 2.16(c, 1H), 2.23-2.38(m, 2H), 2.28-2.54(m, 2H), 4.13(c, 1H), 4.17(d, 1H),
 5.12(c, 1H), 5.15(t, 1H), 5.50(c, 1H), 5.81(s, 1H),
 Found: C, 63.3; H, 7.60%. Calculated for C₂₄H₃₄F₂O₄S: C, 63.1; H, 7.51%].

20 6.5) (20R,S)-9 α -Fluoro-11 β -hydroxy-16 α ,17 α -
butylidenedioxy-17 β -methylthioandrost-4-en-3-one

In an analogous manner 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-3-oxo-9 α -
 fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxyandrost-4-ene-17 β -carboxylate
 25 (2.41g) gives, after purification by low pressure liquid chromatography on silica
 gel eluting with a mixture of diethyl ether and petroleum spirit (9:1) and
 recrystallisation from cyclohexane, (20R,S)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -
 butylidenedioxy-17 β -methylthioandrost-4-en-3-one as a white solid
 (0.58g, 1.32mmol) in a stereoisomeric ratio of 90:10, m.p. 161-163°C;
 30 [NMR(DMSO, d6): 0.89(t, 3H), 1.05(s, 0.3H), 1.14(s, 0.27H), 1.25-1.75(m, 9H),

1.48(s,0.3H),1.49(s,0.27H),1.92-2.10(m,3H),2.03(s,0.3H),2.09(s,0.27H),2.18-2.60(m,6H),4.10(c,1H),4.13(d,0.9H),4.75(d,0.1H), 5.03(c,0.9H),5.06(c,0.1H), 5.10(t,0.1H),5.14(t,1H),5.68(s,1H);
Found: C,65.4;H,8.10%. Calculated for C₂₄H₃₅F₀₄S: C,65.72;H,8.04%].

5

6.6) (20R)-6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -
butylidenedioxy-17 β -fluoromethylthioandrosta-4-en-3-one

By proceeding in a similar manner,(20R)-6 α ,9 α -difluoro-11 β -hydroxy-
10 16 α ,17 α -butylidenedioxy-17 β -methylthioandrosta-4-en-3-one (1.04g,2.28mmol)
gives after work up a white foam (1.05g) which is purified by low pressure liquid
chromatography on silica gel eluting with a mixture of dichloromethane and
methanol (99:1), to give (20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -
butylidenedioxy-17 β -fluoromethylthioandrosta-4-en-3-one (0.11g,0.23mmol),
15 m.p.185-188°C; [NMR(DMSO,d₆): 0.89(t,3H),1.05(s,3H),1.33-1.66(m,7H),
1.49(s,3H),1.73(d,1H),1.85-2.0(m,2H), 2.08(dt,1H),2.19(c,1H),2.03-
2.36(m,2H),2.40-2.52(m,2H),4.15(c,1H),4.39(d,1H),5.10(t,1H),
5.25(d,1H),5.50(c,1H),5.60(dd,1H),5.73(dd,1H), 5.81(s,1H); Found:
C,60.9;H,7.10%. Calculated for C₂₄H₃₃F₃O₄S: C,60.75;H,7.01%].

20

Example 7

7.1) (20R)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-
11 β -hydroxy-17 β -(methylsulphonyl)androsta-1,4-dien-3-one

25

(20R)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
methylthioandrosta-1,4-diene-3-one (3g, 6.6mmol) in solution in acetone (90ml)
is treated dropwise with a solution of potassium peroxymonosulfate (2.1g,
3.36mmol) in water (18ml). After stirring for 40 minutes the reaction mixture is
30 filtered and the filtrate concentrated in vacuo to give a pale yellow gum. This

gum is taken up in chloroform (200ml), washed with water (two times 200ml) and brine (200ml), dried over magnesium sulfate and concentrated in vacuo to give a pale yellow foam. This foam is purified by low pressure liquid chromatography on silica gel to give (20R)-16 α , -17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylsulphinyl)androsta-1,4-dien-3-one as a white solid (0.65g, 1.4mmol), m.p. 179-180°C; [NMR(DMSO, d₆): 0.87(t, 3H), 1.03(s, 3H), 1.30-1.48(m, 3H), 1.49(s, 3H), 1.49-1.82(m, 5H), 1.85-2.0(m, 2H), 2.29(c, 1H), 2.54-2.70(m, 1H), 2.63(s, 3H), 4.15(c, 1H), 5.12(d, 1H), 5.41(c, 1H), 5.47(c, 1H), 5.65(c, 1H), 6.10(s, 1H), 6.29(dd, 1H), 7.25(dd, 1H); Found: C, 61.2; H, 6.91%. Calculated for C₂₄H₃₂F₂O₅S: C, 61.3; H, 6.85%].

7.2) (20R)-9 α -Fluoro-11 β -hydroxy-16 α , 17 α -butylidenedioxy-
17 β -methylsulphinylandrosta-1,4-dien-3-one

15 (20R)-9 α -Fluoro-11 β -hydroxy-16 α , 17 α -butylidenedioxy-17 β -methylthioandrosta-1,4-dien-3-one (1g, 2.3mmol) as starting material gives in an analogous manner to that described above (20R)-9 α -fluoro-11 β -hydroxy-16 α , 17 α -butylidenedioxy-17 β -methylsulphinylandrosta-1,4-dien-3-one as a white solid (0.25g, 0.55mmol), m.p. 175°C; [NMR(DMSO, d₆): 0.87(t, 3H), 1.04(s, 3H), 1.28-1.43(m, 3H), 1.43-1.99(m, 8H), 1.49(s, 3H), 2.35(dd, 1H), 2.35-2.70(m, 2H), 2.65(s, 3H), 4.15(c, 1H), 5.10(d, 1H), 5.32(c, 1H), 5.48(t, 1H), 6.03(s, 1H), 6.23(dd, 1H), 7.27(d, 1H); Found: C, 63.4; H, 7.40%. Calculated for C₂₄H₃₃F₂O₅S: C, 63.7; H, 7.35%].

Example 88.1) (20R)-6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -
butylidenedioxy-17 β -methylsulphonylandrosta-1,4-dien-3-one

5 (20R)-6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -
methylsulphonylandrosta-1,4-dien-3-one (0.3g,0.64mmol) in solution in
chloroform (20ml) is treated at 25°C with 3-chloroperoxybenzoic acid (0.24g,
1.4mmol) and the mixture is stirred for 1 hour. The reaction mixture is treated
10 with an aqueous solution of sodium sulfite then washed successively with water
(two times 25ml), an aqueous solution of sodium carbonate (2M, two times
25ml), water (25ml), and brine (25ml), then dried over magnesium sulfate and
concentrated in vacuo to give a colorless foam which is triturated in hot
diisopropyl ether to give (20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -
15 butylidenedioxy-17 β -methylsulphonylandrosta-1,4-dien-3-one as a white solid
(0.2g,0.41mmol),m.p.149-150°C; [NMR(DMSO,d6): 0.87(t,3H),1.29(s,3H),1.29-
1.48 (m,3H),1.50(s,3H),1.53-1.60(m,2H),1.66-1.77 (m,2H),1.87(d,1H),1.90-
2.05(m,2H),2.29(c,1H), 2.60-2.76(m,1H),3.0(s,3H),4.20(c,1H),4.49(d,1H),
5.46(t,1H),5.50(c,1H),5.65(c,1H),6.12(s,1H), 6.30(dd,1H),7.27(dd,1H); Found:
20 C,58.8;H,6.61%. Calculated for C₂₄H₃₂F₂O₆S: C,59.2;H,6.63%].

Example 99.1) 9 α -Fluoro-11 β -hydroxy-16 α ,17 α -isopropylidene-
25 dioxy-17 β -methylsulphonylandrosta-1,4-dien-3-one

9 α -Fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -
methylthioandrosta-1,4-dien-3-one (1.4g,3.3mmol) in solution in chloroform
(150ml) is treated with 3-chloroperoxybenzoic acid (2.2g,6.8mmol) at 25°C.
30 When the reaction is completed (t.l.c.), the reaction mixture is worked up as
described above and the residue obtained is purified by low pressure liquid

chromatography on silica gel, eluting with a mixture of chloroform and methanol (95:5). Recrystallization from a mixture of acetone and hexane gives 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -methylsulphonylandrosta-1,4-dien-3-one as a white powder (0.24g,0.53mmol), m.p. 180°C (dec.);
5 [NMR(DMSO,d6): 1.29(s,3H),1.29-1.42(m,1H), 1.44(s,3H),1.50(s,3H), 1.52(s,3H), 1.59(dd,1H),1.73-1.88(m,3H),1.99(dt,1H),2.10(dt,1H),2.35(dd,1H), 2.49-2.70(m,2H), 2.96(s,3H),4.18(c,1H),5.15(d,1H),5.40(c,1H), 6.03(s,1H),6.24(dd,1H),7.28(d,1H); Found: C,61.0;H,7.00%. Calculated for C₂₃H₃₁F₀₆S: C,60.7;H,6.90%].

10

Example 10

10.1) (20S)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -
hydroxy-17 β -(methylthio)androst-4-ene-3-one

15

A stirred mixture of (20S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-diene-3-one(0.16 g) in ethanol (2 ml) is purged with nitrogen then treated with a catalytic amount of rhodium bis(triphenyl phosphine) chloride. The reaction mixture is stirred under a
20 positive pressure of hydrogen until one equivalent had been taken up. The reaction mixture is washed with water (50 ml) and concentrated in vacuo. The residue is purified by low pressure liquid chromatography on silica gel eluting with ethyl acetate/ cyclohexane 1/1 to give (20S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androst-4-ene-3-one (0.15 g) as an
25 off white powder.

[Found: C, 63.3;H,7.6%

Calculated for C₂₄H₃₄F₂O₄S: C, 63.1; H, 7.51.]

Example 11

11.1) (20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-
11 β -hydroxy-17 β -(methylthio)androst-3-one

5

By proceeding as described in Example 1, 2-thioxo-1,2-dihydropyrid-1-yl
(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrostane-
17 β -carboxylate as starting material affords after work up and low pressure
liquid chromatography on silica gel eluting with ethyl acetate/ cyclohexane 1/1
10 gives (20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androst-3-one (as an off white solid).
[Found: C, 62.6; H, 7.9
Calculated for C₂₄H₃₆F₂O₄S: C, 62.9; H, 7.9]

15 Example 12

12.1) (20R)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -
hydroxy-17 β -(methylthio)androst-4-en-3,6-dione

20

A solution of (20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androst-1,4-diene-3,6-dione (0.15 g) in toluene (2 ml) and ethanol
(2 ml) is purged with nitrogen, treated with rhodium bis(triphenyl phosphine)
chloride (0.015 g) and hydrogenated at 0.3 bar over night, heated at 50°C for 6
hours and left to stand for 3 days. The reaction mixture is concentrated in
25 vacuo and chromatographed on silica gel eluting with ethyl acetate/cyclohexane
1/2 to give (20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)-androst-4-en-3,6-dione (0.08 g) as an off white powder.
[Found: C, 64.0; H, 7.5
Calculated for C₂₄H₃₃FO₅S: C, 63.7; H, 7.35.]

Reference Example 1

5 R. E. 1.1) (20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -
hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid

To a well stirred suspension of 9 α -fluoro-11 α ,16 α ,17 α -trihydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (7.9 g, 20 mmol) in tetrahydrofuran (65 ml) at 25 $^{\circ}$ C is added butyraldehyde (9.2 ml, 100 mmol) and perchloric acid (0.2 g, 1.97 mmol). When the reaction mixture is homogeneous (1-5 hrs), the perchloric acid is neutralized by addition of triethylamine (0.2 g, 1.97 mmol). Evaporation of the solvent in vacuo gives a solid which is dissolved in sodium hydroxide (2 N) and the resulting aqueous solution is washed several times with diethyl ether. Neutralization of this aqueous solution with hydrochloric acid (10 N) gives a white precipitate which is filtered off, washed with water and dried under vacuum at 80 $^{\circ}$ C overnight: (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (8.5 g, 18.3 mmol), m.p. 205 $^{\circ}$ C (dec.); [N.M.R. (DMSO, d6): 0.85 (m, 3H), 0.96 (s, 3H), 1.22-1.46 (c, 4H), 1.50 (s, 3H), 1.49-1.61 (m, 3H), 1.70-1.97 (m, 4H), 2.33 (dd, 1H), 2.34-2.50 (m, 1H), 2.62 (dt, 1H), 4.15 (c, 1H), 4.67 (t, 0.9H), 4.85 (d, 0.9H), 5.08 (d, 0.1H), 5.16 (t, 0.1H), 5.89 (m, 1H), 6.01 (s, 1H), 6.23 (dd, 1H), 7.29 (d, 1H)]. This compound is used in the next step without further purification.

Reference Example 2

25 R. E. 2.1) (20R,S)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-
11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid

To a stirred suspension of 6 α ,9 α -difluoro-11 α ,16 α ,17 α -trihydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (50 g, 126 mmol) in tetrahydrofuran (2 l) at 25 $^{\circ}$ C under a nitrogen atmosphere is added butyraldehyde (59.2 g, 820

mmol) and perchloric acid (1.2 g, 11.8 mmol). The reaction mixture is stirred for 16 hours then treated dropwise with triethylamine (1.2 g, 11.8 mmol).

Evaporation of the solvent in vacuo gives a yellow oil which is partitioned between ethyl acetate (1 l) and sodium carbonate (2 N). The aqueous phase is decanted, washed with more ethyl acetate (400 ml), acidified to pH 2 with hydrochloric acid (10 N) before being extracted with diethyl ether (1 l). The combined diethyl ether extracts were washed with water, brine then dried over magnesium sulfate. Filtration of the dessicant and evaporation of the solvent in vacuo gives a white solid which is triturated with cyclohexane before being dried under vacuum at 80°C overnight: (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (54.8 g, 121 mmol); [N.M.R. (DMSO, d6): 0.85 (m, 3H), 0.96 (s, 3H), 1.22-1.46 (c, 4H), 1.50 (s, 3H), 1.49-1.62 (m, 3H), 1.79 (c, 1H), 1.90-2.06 (m, 3H), 2.26 (c, 1H), 2.45-2.67 (m, 1H), 4.17 (c, 1H), 4.68 (t, 0.8H), 4.88 (d, 0.8H), 5.10 (d, 0.2H), 5.19 (t, 0.2H), 5.45 (d, 1H), 5.63 (c, 1H), 6.10 (s, 1H), 6.29 (dd, 1H), 7.35 (d, 1H)]. This compound is used in the next step without further purification.

R. E. 2.2) (20R,S)-16 α ,17 α -[(E)-2-Butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid

In an analogous manner using 9 α -fluoro-11 α ,16 α ,17 α -trihydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (8.9 g, 23.4 mmol) and crotonaldehyde (7.4 g, 105.3 mmol) as starting materials gives after work up (20R,S)-16 α ,17 α -[(E)-2-butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (9.1 g, 21 mmol); [N.M.R. (DMSO, d6): 0.96 (s, 3H), 1.30-1.43 (m, 1H), 1.50 (s, 3H), 1.47-1.60 (m, 2H), 1.64 (dd, 0.6H), 1.68 (dd, 2.4H), 1.68-2.0 (m, 5H), 2.34 (dd, 1H), 2.35-2.52 (m, 1H), 2.64 (dt, 1H), 4.15 (c, 1H), 4.85 (d, 0.8H), 4.97 (d, 0.8H), 5.07 (d, 0.2H), 5.28 (ddd, 0.2H), 5.33-5.40 (m, 1.8H), 5.46 (d, 0.2H), 5.85 (m, 0.2H), 5.92 (m, 0.8H), 6.03

(s, 1H), 6.23 (dd, 1H), 7.29 (d, 1H)]. This compound is used as such in the next step.

5 R. E. 2.3) (20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -
hydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylic acid

By proceeding in an analogous manner but using 9 α -fluoro-11 β ,16 α ,17 α -trihydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylic acid (2.1 g) gives after work up (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3,6-
10 dioxoandrosta-1,4-diene-17 β -carboxylic acid (1.6 g); [N.M.R. (DMSO, d₆): 0.8-0.9 (m, 3H), 0.97 (s, 3H), 1.2-1.45 (m, 3H), 1.47 (s, 3H), 1.48-1.65 (m, 3H), 1.8-1.9 (m, 1H), 2-2.2 (m, 2H), 2.25-2.35 (m, 1H), 2.6-2.95 (m, 2H), 4.2-4.3 (c, 1H), 4.68 (t, 0.8H), 4.88 (d, 0.8H), 5.1 (d, 0.2H), 5.23 (t, 0.2H), 5.52 (c, 0.2H), 5.62 (c, 0.8H), 6.29 (d, 1H), 6.4 (dd, 1H), 7.41 (2d, 1H)].

15 R. E. 2.4) (20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -
hydroxy-3-oxoandrost-4-ene-17 β -carboxylic acid

9 α -Fluoro-11 β -16 α ,17 α -trihydroxy-3-oxoandrost-4-ene-17 β -carboxylic acid
20 (2.4 g) gives in a manner analogous to that described above (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrost-4-ene-17 β -carboxylic acid (2.15 g).

Reference Example 3

25 R. E. 3.1) 9 α -Fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid

9 α -Fluoro-11 α ,16 α ,17 α -trihydroxy-3-oxoandrosta-1,4-diene-17 β -
30 carboxylic acid (7.9 g, 20 mmol) is suspended in acetone (100 ml) then

perchloric acid (0.2 g, 1.97 mmol) is added at 25°C. 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid is isolated after work up as a white solid (7 g, 16.7 mmol) in a manner analogous to that described above, m.p. 316°C (dec.); [N.M.R. (DMSO, d6): 0.94 (s, 3H), 1.15 (s, 3H), 1.20 (s, 3H), 1.26-1.40 (m, 1H), 1.49 (s, 3H), 1.47-1.51 (m, 1H), 1.53-1.62 (dt, 1H), 1.68 (d, 1H), 1.69-1.95 (m, 3H), 2.33 (dd, 1H), 2.35-2.52 (m, 1H), 2.64 (dt, 1H), 4.15 (c, 1H), 4.95 (d, 1H), 6.34 (m, 1H), 6.02 (s, 1H), 6.21 (dd, 1H), 7.27 (d, 1H)] which is used as such in the next step.

10 R. E. 3.2) 6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid

In an analogous manner 6 α ,9 α -difluoro-11 α ,16 α ,17 α -trihydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (45.0 g, 112.9 mmol) gives after work up 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (40.9 g, 93.3 mmol), m.p. 285-7°C (dec.); [N.M.R. (DMSO, d6): 0.93 (s, 3H), 1.15 (s, 3H), 1.31 (s, 3H), 1.40-1.67 (m, 4H), 1.50 (s, 3H), 1.69 (d, 1H), 1.80-2.02 (m, 2H), 2.26 (c, 1H), 2.48-2.65 (m, 1H), 4.17 (c, 1H), 4.97 (d, 1H), 5.43 (c, 1H), 5.64 (m, 1H), 6.10 (s, 1H), 6.28 (dd, 1H), 7.27 (dd, 1H)] which is used as such in the next step.

Reference Example 4

25 R. E. 4.1) 9 α -Fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride

To a stirred solution of 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (1.05 g, 2.5 mmol) in tetrahydrofuran (35 ml) containing activated molecular sieve (type 4 A,

1 g) at 25°C under an atmosphere of nitrogen is added triethylamine (0.7 ml, 5 mmol). After stirring for 0.5 hour the reaction mixture is treated with diethyl chlorophosphate (0.54 ml, 3.75 mmol) over a period of 45 minutes and stirred for a further 90 minutes. The resulting mixture is filtered through a pad of celite
5 and the tetrahydrofuran evaporated in vacuo, the crude oil obtained is taken up in ethyl acetate (50 ml), washed with hydrochloric acid (1 N, 25 ml) then with water (two times 25 ml) and brine (two times 25 ml). The ethyl acetate phase is dried over sodium sulphate, the dessicant is then filtered off and concentration in vacuo affords the 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride as a crude
10 yellow oil (1.5 g) which is used without further purification in the next step.

R. E. 4.2) 6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -
isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic
15 diethyl phosphoric anhydride I

6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (7.04 g, 16 mmol) gives in a manner analogous to that described above 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -
20 isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride as a crude white foam (9.8 g) which is used as such in the next step.

R. E. 4.3) (20R,S)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-
11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic
25 diethyl phosphoric anhydride

(20R,S)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (14.5 g, 32 mmol) gives in a manner analogous to that described above (20R,S)-16 α ,17 α -butylidenedioxy-

6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride (19.5 g crude) which is used as such in the next step.

- 5 R. E. 4.4) (20R,S)-16 α ,17 α -[(E)-2-Butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride

(20R,S)-16 α ,17 α -[(E)-2-Butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (10.0 g, 23.1 mmol) gives in an
10 manner analogous to that described above (20R,S)-16 α ,17 α -[(E)-2-butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride (13 g crude) which is used without further purification in the next step.

- 15 R. E. 4.5) (20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl-phosphoric anhydride

In an analogous manner using (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-
20 11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (6.4 g, 15.2 mmol) as starting material gives the crude (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride as a crude yellow oil (7.5 g) which is used as such in the next step.

- 25 R. E. 4.6) (20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride

In an analogous manner using (20R,S)-16 α ,17 α -butylidenedioxy-9 α -
30 fluoro-11 β -hydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylic acid (1.46 g)

gives in a manner analogous to that described above (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride (2.06 g crude).

- 5 R. E. 4.7) (20R)-6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-3-oxoandrosta-17 β -carboxylic acid
diethyl phosphoric anhydride

(20R)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-17 β -carboxylic acid(2 g) gives in a manner analogous to that described above (20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-3-oxoandrosta-17 β -carboxylic acid diethyl phosphoric anhydride.

- 15 R. E. 4.8) (20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-4-ene-17 β -carboxylic diethyl phosphoric
anhydride

(20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-4-ene-17 β -carboxylic acid (2.1 g) gives in a manner analogous to that described above (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-4-ene-17 β -carboxylic diethyl phosphoric anhydride (2.8 g).

Reference Example 5

- 25 R. E. 5.1) 2-Thioxo-1,2-dihydropyrid-1-yl 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylate

In a reaction vessel protected from light, a stirred solution of 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic

diethyl phosphoric anhydride (3.4 g) in dimethyl-formamide (30 ml) containing activated molecular sieve (type 4 A, 5 g) and maintained at 20°C under a nitrogen atmosphere is treated with the sodium salt of 2-mercaptopyridine N-oxide (1.13 g, 7.6 mmol). After the reaction is completed (t.l.c.), the reaction mixture is filtered and the filtrate poured into ice cold water (150 ml). The yellow precipitate formed is collected by filtration, washed with cold water then taken up in dichloromethane (100 ml), washed with cold water, brine then dried over sodium sulphate. The dessicant is filtered off, the clear yellow solution concentrated in vacuo (20°C; 13 mmHg) to give a bright yellow precipitate of 2-thioxo-1,2-dihydropyrid-1-yl 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (2.5 g) which is used as such in the next step. All the above procedures are carried out with exclusion of light as far as is practicable.

15 R. E. 5.2) 2-Thioxo-1,2-dihydropyrid-1-yl 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylate

20 6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride (9.7 g) gives in a manner analogous to that described above 2-thioxo-1,2-dihydropyrid-1-yl 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (8.41 g) which is used as such in the next step.

25 R. E. 5.3) 2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17- α butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate

30 (20R,S)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride (19.5 g)

gives after work up 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (19.5 g) which is used in the next step without further purification.

R. E. 5.4) 2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -[(E)-2-butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate

5 (20R,S)-16 α ,17 α -[(E)-2-Butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride. (2 g) gives after work up 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -[(E)-2-butenylidenedioxy]-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (1.90 g) which is used as such in the next step.

10

R. E. 5.5) 2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate

15 An analogous procedure using diethyl (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride (4.2 g) as starting material affords 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (3 g) which is used in the next step

20 without further purification.

R. E. 5.6) 2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylate

25

An analogous procedure using (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylic diethyl phosphoric anhydride (2.0 g) gives after work up 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylate (1.83 g).

30

R. E. 5.7) 2-Thioxo-1,2-dihydropyrid-1-yl (20R)-16 α ,17 α -
butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-
oxoandrostane-17 β -carboxylate

5

(20R)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-
oxoandrostane-17 β -carboxylic diethyl phosphoric anhydride gives in a manner
analogous to that described above 2-thioxo-1,2-dihydropyrid-1-yl (20R)-
16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrostane-17 β -
10 carboxylate.

R. E. 5.8 2-Thioxo-1,2-dihydropyrid-1-yl (20R,S)-16 α ,17 α -
butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrost-4-
ene-17 β -carboxylate

15

(20R,S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrost-4-
ene-17 β -carboxylic diethyl phosphoric anhydride (2.8 g) gives in a manner
analogous to that described above 2-thioxo-1,2-dihydropyrid-1-yl (20R,S)-
16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-3-oxoandrost-4-ene-17 β -
20 carboxylate (2.4 g).

Reference Example 6

R. E. 6) 9 α -Fluoro-11 β ,16 α ,17 α -trihydroxy-3,6-
 dioxoandrosta-1,4-diene-17 β -carboxylic acid

5 To a stirred mixture of 9 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregna-1,4-
diene-3,6,20-trione (2.4 g) in dry dimethylformamide is added potassium
superoxide (1.68 g) followed by 18-crown-6 (1.56 g). The reaction temperature
rose to 48°C and is cooled to 40°C. The reaction mixture is added to water
10 (300 ml), acidified to pH 9, washed with ethyl acetate (2 times) and acidified to
pH 2 (using concentrated hydrochloric acid) then extracted into ethyl acetate (3
times). The combined organic extracts were washed with brine then dried over
magnesium sulfate. Filtration of the dessicant and concentration in vacuo gives
9 α -fluoro-11 β ,16 α ,17 α -trihydroxy-3,6-dioxoandrosta-1,4-diene-17 β -carboxylic
15 acid as an orange powder upon trituration with ethyl acetate (0.7 g). This is used
as such in the next step.

Reference Example 7

20 R. E. 7.1) 9 α -Fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregna-1,4-
 diene-3,6,20-trione

 A stirred suspension of 21-acetyloxy-9 α -fluoro-11 β ,16 α ,17 α -
trihydroxypregna-1,4-diene-3,6,20-trione (4.32 g) in degassed methanol (200
25 ml) and tetrahydrofuran (50 ml), under an inert atmosphere is treated with a
solution of potassium carbonate (0.62 g) in water (10 ml) over one hour. The
reaction mixture is acidified to pH 6 (dilute hydrochloric acid), cooled to 0°C
and the precipitated solid filtered off and washed with cold methanol to give 9 α -
fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregna-1,4-diene-3,6,20-trione (2.78 g) as a
30 buff powder m.p. 255-6°C.

Reference Example 8

R. E. 8.1) 21-Acetyloxy-9 α -fluoro-11 β ,16 α ,17 α -trihydroxy-
pregna-1,4-diene-3,6,20-trione

5

A stirred solution of 21-Acetyloxy-9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-pregna-1,4-diene-3,6,20-trione (6.7 g) in formic acid (200 ml), under an inert atmosphere is heated at 70-75°C for 6 hours and left to stand over night. The reaction mixture is concentrated in vacuo, taken up in
10 toluene, and concentrated in vacuo again. The residue is suspended in methanol (40 ml) and treated slowly with concentrated ammonia solution until the pH of the reaction mixture is 9 or 10. The mixture is cooled to 0°C and the precipitated solid filtered off, washed with cold methanol, and sucked dry to give
15 21-acetyloxy-9 α -fluoro-11 β ,16 α ,17 α -trihydroxypregna-1,4-diene-3,6,20-trione (4.32 g) as a pale yellow powder.

Reference Example 9

R. E. 9.1) (20R)-6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -
20 butylidenedioxy-3-oxoandrostane-17 β -carboxylic acid

A stirred mixture of (20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxoandrost-4-ene-17 β -carboxylic acid (5 g) in ethanol (100 ml) is purged with nitrogen, treated with 5% palladium on charcoal (5 g) and then
25 hydrogenated at 0.3 bars for several hours. The reaction mixture is filtered through celite and the filtrate concentrated in vacuo to give (20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-3-oxoandrostane-17 β -carboxylic acid (4.7 g) as a white foam.

Reference Example 10

R. E. 10.1) 9α -Fluoro- 11β - 16α , 17α -trihydroxy-3-oxoandrost-4-ene- 17β -carboxylic acid

5 To a stirred mixture of 9α -fluoro- 11β - 16α , 17α -21-tetrahydroxypregn-4-ene-3,20-dione (2 g) in dry dimethylformamide (30 ml) is added potassium superoxide (1.4 g) followed by 18-crown-6 (1.3 g) and cooling used to maintain the temperature at 25-38°C. The reaction mixture is stirred for 1/2 an hour,
10 treated with water (300 ml), acidified to pH 9, washed with ethyl acetate (2 times) then acidified to pH 2 (using concentrated hydrochloric acid) and extracted with ethyl acetate (3 times). The combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration of the dessicant and concentration in vacuo gives α -fluoro- 11β - 16α , 17α -trihydroxy-3-
15 oxoandrost-4-ene- 17β -carboxylic acid (0.9 g) as a white solid .

The present invention also includes within its scope pharmaceutical formulations which comprise an effective amount of at least one of the
20 compounds of formula I in association with a pharmaceutically acceptable carrier or coating.

PHARMACOLOGICAL USES

25 An object of the invention is to provide a topical antiinflammatory, immunosuppressive and antiallergic steroid, or a pharmaceutical composition thereof, for the following:

topical treatment of skin conditions such as dermatitis, psoriasis,
30 sunburn, eczema, neurodermatitis and anogenital pruritis;

inhaled treatment of airways conditions such as allergy, asthma and rhinitis, chronic obstructive pulmonary disease, interstitial lung diseases and fibrosis;

5 local treatment of inflammatory bowel conditions such as ulcerative colitis and Crohn's disease; and

 local treatment of conjunctiva and conjunctivitis.

10 The topical treatment of such conditions by steroid compounds of this invention is associated with no side-effects or minimal side-effects associated with typical systemic steroid activity, such as suppression of hypothalamus-pituitary-adrenal function, mobilisation of glucose stores, collagen disorders, mineralocorticoid function, adrenal atrophy, osteoporosis and suppression of
15 bone growth and atrophy of thymic tissue.

 This may be achieved by a combination of direct delivery of the steroid to the application site, and by reduced systemic activity, caused by restricted absorption or by rapid in-vivo metabolism of the steroid. Thus, inactivation of
20 the steroid can be by metabolism in the target organ or, after uptake into the general circulation, e.g. by metabolism or excretion. Such compounds are often referred to as "soft" steroids.

PHARMACOLOGICAL TEST SYSTEMS

Biological test results on compounds of this invention are exemplified as follows:

5

GLUCOCORTICOID AGONIST ACTIVITY

STEROID BINDING TO THE RAT THYMUS GLUCOCORTICOID RECEPTOR

10 Thymi of male adrenalectomised rats are removed and homogenised in 3-(N-morpholino)propanesulphonic acid dithiothreitol buffer, and centrifuged at 100,000g. The supernatant cytosol is used as the source of receptor. Steroid (1-16nM in doubling dilutions) and [³H] dexamethasone (4nM) are equilibrated with receptor for 24 hours at 4°C. Bound [³H] dexamethasone is separated
15 from free dexamethasone by a dextran coated charcoal technique and is quantified by liquid scintillation counting. The IC₅₀ (concentration reducing [³H] dexamethasone binding by 50%) is calculated from the plot of the fraction bound against added steroid concentration.

20 The following results demonstrate the effectiveness of compounds of this invention when subjected to the above glucocorticoid receptor binding assay:

9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -methylthioandrosta-1,4-dien-3-one	1.6nM
(20R)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -methylthioandrosta-1,4-dien-3-one	1.7nM

(20R,S)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -(2-pyridylthio)androsta-1,4-dien-3-one	11.3 nM
9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -methylsulphonylandrosta-1,4-dien-3-one	3.8 nM
(20R)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -methylsulphonylandrosta-1,4-dien-3-one	6.6 nM
6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -methylthioandrosta-1,4-dien-3-one	3.2 nM
(20R)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -(E)-butenylidenedioxy-17 β -methylthioandrosta-1,4-dien-3-one	2.6 nM
(20R,S)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -isopropylthioandrosta-1,4-dien-3-one	5.5 nM
(20R,S)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -ethylthioandrosta-1,4-dien-3-one	4.1 nM
(20R)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -fluoromethylthioandrosta-1,4-dien-3-one	7.5 nM
(20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -methylthioandrosta-1,4-dien-3-one	3.7 nM
6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -fluoromethylthioandrosta-1,4-dien-3-one	4.1 nM

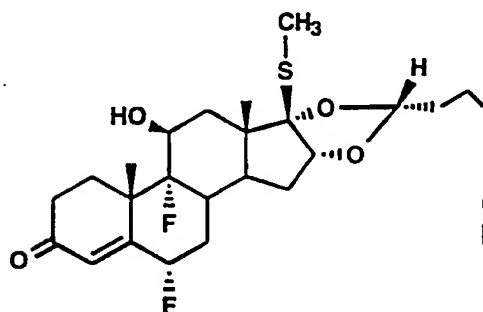
(20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylenedioxy-17 β -fluoromethylthioandrosta-4-en-3-one	0.3 nM
(20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylenedioxy-17 β -fluoromethylthioandrosta-1,4-dien-3-one	2.7 nM
(20S)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylenedioxy-17 β -fluoromethylthioandrosta-1,4-dien-3-one	2.5 nM
(20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylenedioxy-17 β -methylthioandrosta-4-en-3-one	2.9 nM to 3.2nM
(20R)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylenedioxy-17 β -methylthioandrosta-1,4-dien-3,6-dione	2.4 nM
(20R,S)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -butylenedioxy-17 β -methylthioandrost-4-en-3-one (stereoisomeric ratio 90:10)	2.5 nM
9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(2-pyridylthio)androsta-1,4-dien-3-one	27 nM
(20S)-16 α ,17 α -butylenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androst-4-ene-3-one	2.9 nM
(20R)-16 α ,17 α -butylenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androstan-3-one	2.6 nM
(20R)-16 α ,17 α -butylenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(methylthio)androst-4-en-3,6-dione	3.4 nM

Further tests which demonstrate the effectiveness of compounds of this invention are as follows. The following representative compound illustrates the pharmacological activity present with compounds of this invention.

5

Structure:

Name:



(20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -
butylienedioxy-17 β -methylthioandrosta-4-en-3-one

10

INHIBITION OF TUMOUR NECROSIS FACTOR (TNF- α) RELEASE FROM HUMAN PERIPHERAL BLOOD MONOCYTES

15

20

Monocytes are obtained from blood samples taken from normal human donors. The leukocyte population is washed, applied to a discontinuous metrizamide gradient, and fractionated by centrifugation. The monocyte-enriched interface is aspirated, the cells washed and total and differential counts performed to determine the number of monocytes. Cells are allowed to adhere to 96-well plates for 1 to 2 hours, and thereafter incubated (8x10⁵ monocytes/well) with the steroid for 18 hours (37°C in 5% CO₂). Cells are challenged with 10ng/ml lipopolysaccharide for 4 hours and TNF- α is assayed by use of an enzyme-linked immunosorbent assay. TNF- α quantification is performed with goat anti-human TNF- α being used as the coating antibody, rabbit anti-human TNF- α as the second antibody, and goat anti-rabbit IgG horseradish peroxidase as the detection antibody. The IC₅₀ is the steroid concentration reducing TNF- α release by 50%. IC₅₀=0.25nM

INDUCTION OF TYROSINE AMINOTRANSFERASE ACTIVITY

Rat liver H4IIE cells are cultured for 4 days until the cells are confluent. The medium is replaced by fresh medium, containing steroid under test (0-
5 100nM) which is added to triplicate wells. After overnight incubation as above, the medium is removed and the cells are lysed and the extract is equilibrated at 37°C with α -ketoglutarate and pyridoxal phosphate in phosphate buffer, pH 7.3, in a final volume of 1ml. Tyrosine aminotransferase activity is initiated by
10 adding tyrosine and incubating at 37°C for 10 minutes. The reaction is stopped by adding aqueous sodium hydroxide solution (10M). The ultra-violet absorbance of the para-hydroxybenzaldehyde is measured by a plate reader at 340nm. The maximal absorbance change achieved with the standard (dexamethasone) is used as a reference. The absorbance change for each
15 concentration of steroid under test is calculated as a fraction of the maximal absorption achievable and plotted against steroid concentration. The ED₅₀ is determined as the concentration causing an increase in tyrosine aminotransferase activity of 50% of the maximum achievable.
IC₅₀=0.3nM

INHIBITION OF RAT LUNG OEDEMA IN-VIVO:

Test compounds are suspended in 1% carboxymethyl-cellulose/0.2% Tween 80 at double the required strength and sonicated to form a suspension.

- 5 This is administered intra-tracheally (i.t.) to male rats (Sprague-Dawley strain, 6 in each group, each weighing about 350g) at 0 hours and 24 hours, with the first dose being co-administered with saline and the second with Sephadex G200 [cross-linked dextran] (10mg/ml) giving a final Sephadex concentration of 5mg/ml. I.t. dosing is carried out under halothane anaesthesia (4% in oxygen, 10 at 4 litres/minute for 3 minutes). At 48 hours, the rats are killed, final body weight is recorded, and the lungs and thymus are removed and weighed. The doses reducing the Sephadex-induced oedema and the thymus weight by 30% (ED₃₀) are calculated. Airway selectivity is defined as the ratio of thymus involution (ED₃₀) and inhibition of lung oedema (ED₃₀).

- 15 Lung oedema: ED₃₀ = 0.003 mg/kg

Thymus involution: ED₃₀ = 2.2 mg/kg

Airway selectivity: 733.

20

INHIBITION OF MOUSE EAR OEDEMA IN-VIVO

- (i) Steroids are dissolved in acetone and administered epicutaneously to the ventral and dorsal surfaces of the right ear pinna of female mice (CD1 strain, 25 5 in each group, each weighing about 20g). 18 Hours later, phorbol myristate acetate (PMA, 1.25µg/ear) in acetone is applied epicutaneously to the right ear. The mice are killed 4 hours later, and a 5mm disc is punched out of each ear and weighed. The dose reducing PMA-induced oedema by 50% (ED₅₀) is determined from linear regression.

- 30 Inhibition of PMA-induced mouse ear oedema: ED₅₀ = 0.0082 µg/ear

(ii) Ovalbumin sensitised mice are challenged with antigen injected into the right ear intradermally under 4% halothane anaesthesia (4% in oxygen, 4 litres/minute for 2 minutes) 18 hours after topical treatment with the steroids [as above in (i)]. The mice are killed 1 hour later, and a 5mm disc is punched out of each ear, and weighed. The dose reducing the oedema by 50% (ED₅₀) is determined as above.

Inhibition of antigen-induced mouse ear oedema: ED₅₀ = 0.026 µg/ear

In view of the results obtained when compounds of the present invention are subjected to the above tests, it can be demonstrated that valuable properties for the relief of inflammation are indicated.

In clinical practice the compounds are administered in a form suitable for the area of the body to be treated. For example, for the treatment of diseases of the respiratory system they are usually administered as aerosols or, preferably, as dry powder formulations, and for the treatment of diseases of the skin they are usually administered as creams, ointments or lotions. Such formulations are prepared by the application or adaptation of known methods such as the following.

PHARMACEUTICAL COMPOSITIONS

For the topical treatment of skin conditions, the steroids may be administered in a conventional pharmaceutical carrier such as creams, ointments, lotions, emulsions, solutions, foams, or the like.

The steroid compounds of this invention may be used for topical treatment of skin conditions, in the range of about 0.0001 to about 5%, preferably about 0.01 to about 2%, by weight of the vehicle.

For the topical treatment of allergy and asthma the steroids may be administered as a dry powder, for example in a single dose inhaler or a multidose inhaler, or as a suspension or a solution in a metered dose aerosol unit or in a nebuliser, with a suitable carrier, or the like. Such devices are well known in the art and standard modes of preparation may be employed or adapted.

Such formulations for inhalation typically contain from about 10 to about 4,000, preferably from about 100 to about 1,600, μg per dose.

10

Still further, steroids of this invention may be administered in anal or peri-anal formulations, e.g. foams, solutions or suspensions and suppositories. Such formulation techniques are well known in the art.

15 An example of a formulation as a retention enema for the treatment of ulcerative colitis (this can also be a continuous drip, i.e. a solution formulation) can be found in the specification of U S Patent 4,710,495.

20 Formulation as liposomes may be used as described in the specification of WO 92/13873.

Slow release oral formulations such as formulations for release into the intestine or colon or both, e.g. slow release tablets, may also be employed.

25 Such oral and anal or peri-anal formulations are typically administered so as to deliver from about 0.1 to about 100, preferably from about 5 to about 50, mg per day.

30 The following Composition Example illustrates pharmaceutical compositions according to the present invention.

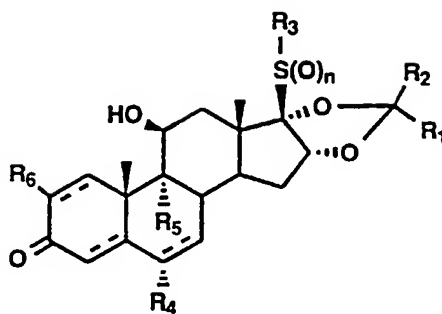
COMPOSITION EXAMPLE 1

(20R)-6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α - butylidenedioxy-17 β -
methylthioandrosta-4-en-3-one (1.0g) (mean particle size 3.5 microns) and
5 lactose (99g) (mean particle size 72 microns) are blended together for 30
minutes in a mechanical shaker/mixer. The resulting blend is filled, to a fill
weight of 25mg, into No.3 hard gelatine capsules, to give a product suitable for
use, for example, with a dry powder inhaler.

CLAIMS

1. A compound of the formula:

5



where:

----- is independently at each of the 1,2-, 4,5- and 6,7-positions, a single or double bond;

10 R₁ is a straight- or branched-chain C₁₋₄ alkyl or C₂₋₄ alkenyl;

R₂ is hydrogen or methyl;

R₃ is C₁₋₇ alkyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl or -CH₂R where R is halo, hydroxy, C₁₋₅ alkoxy or C₁₋₁₀ alkanoyloxy;

15 R₄ is hydrogen, halo, hydroxy, keto or C₁₋₃ alkoxy when ----- at the 6,7-position forms a single bond, or hydrogen, halo or C₁₋₃ alkoxy when

----- at the 6,7- position forms a double bond;

R₅ is hydrogen or halo;

R₆ is hydrogen when ----- at the 1,2-position forms a single bond or


20 hydrogen or chloro when ----- at the 1,2-position forms a double bond; and

n is 0-2; and

racemic mixtures and diastereoisomers thereof.


2. A compound according to Claim 1

where:


5  is a double bond at the 1,2- and 4,5-positions and a single bond
at the 6,7-position;
R₁ is alkyl or alkenyl;
R₂ is hydrogen, or methyl;
R₃ is alkyl, haloalkyl or heteroaryl;
R₄ is hydrogen, halo, or keto ;
10 R₅ is halo;
R₆ is hydrogen; and
n is 0-2.

15 3. A compound according to Claim 2

where:

 is a double bond at the 1,2- and 4,5-positions and a single bond
at the 6,7-position;
R₁ is methyl, propyl or trans-prop-1-enyl ;
20 R₂ is hydrogen, or methyl;
R₃ is methyl, isopropyl, fluoromethyl or pyridyl;
R₄ is hydrogen, fluoro, or keto ;
R₅ is fluoro;
R₆ is hydrogen; and
25 n is 0-2.


4. A compound according to Claim 1
where:

 is a double bond at the 4,5-position and single bonds at the 1,2-
and 6,7-positions;

- 5 R₁ is alkyl or alkenyl;
 R₂ is hydrogen, or methyl;
 R₃ is alkyl, haloalkyl or heteroaryl;
 R₄ is hydrogen, halo, or keto ;
 R₅ is halo;
10 R₆ is hydrogen; and
 n is 0-2.

5. A compound according to Claim 4

15 where:

 is a double bond at the 4,5-position and a single bond at the 1,2-
and 6,7-positions;

- R₁ is methyl, propyl or trans-prop-1-enyl ;
 R₂ is hydrogen, or methyl;
20 R₃ is methyl, fluoromethyl or pyridyl;
 R₄ is hydrogen, fluoro, or keto ;
 R₅ is fluoro;
 R₆ is hydrogen; and
 n is 0-2.

25

6. A compound according to Claim 3 which is

 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -
30 (methylthio)androsta-1,4-dien-3-one;

9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -
(methylsulphonyl)androsta-1,4-dien-3-one;

5 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(2-
pyridylthio)androsta-1,4-dien-3-one;

6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -
(methylthio)androsta-1,4-dien-3-one; and

10

6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-17 β -(fluoro-
methylthio)androsta-1,4-dien-3-one.

15 7. A compound according to Claim 3 selected from:

(20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-dien-3-one;

20 (20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(2-pyridyl-
thio)androsta-1,4-dien-3-one;

(20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylsulphonyl)androsta-1,4-dien-3-one;

25

(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(isopropylthio)androsta-1,4-dien-3-one;

(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
30 methylthioandrosta-1,4-dien-3-one;

(20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(fluoromethylthio)androsta-1,4-dien-3-one;

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
5 (methylthio)androsta-1,4-dien-3-one;

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylsulphonyl)androsta-1,4-dien-3-one;

10 (20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(fluoromethylthio)androsta-1,4-dien-3-one;

(20R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androsta-1,4-dien-3-one;

15 (20S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylsulphonyl)androsta-1,4-dien-3-one; and

(20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
20 (methylthio)androsta-1,4-diene-3,6-dione.

8. A compound according to Claim 3 which is (20R)-16 α ,17 α -[(E) 2-
butenyldenedioxy]-9 α -fluoro-11 β -hydroxy-17 β -(methylthio)androsta-1,4-dien-3-
25 one.

9. A compound according to Claim 5 selected from:

(20R,S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -
(methylthio)androst-4-en-3-one;

5

(20R)-16 α ,17 α --butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(fluoro-
methylthio)androst-4-en-3-one;

10 (20R)-16 α ,17 α --butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -
(methylthio)androst-4-en-3-one; and

(20R)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β -hydroxy-17 β -(methylthio)-
androst-4-ene-3,6-dione.

15

10. A compound according to Claim 1 where the 1,2-, 4,5- and 6,7- positions
are all single bonds.

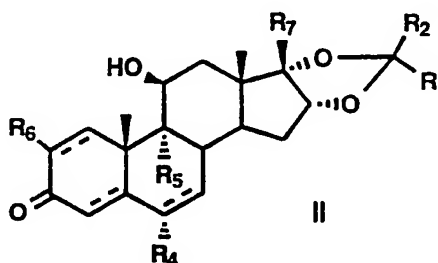
20 11. A compound according to Claim 10 which is (20R)-16 α ,17 α -butylidene-
dioxy-6 α ,9 α -difluoro-11 β -hydroxy-17 β -(methylthio)androstan-3-one.

25 12. A method for the treatment of a patient in need of an antiinflammatory,
immunosuppressive or antiallergic treatment which comprises administering to
said patient an effective antiinflammatory, immunosuppressive or antiallergic
amount of a steroid compound of Claim 1.

30 13. A pharmaceutical composition which comprises a steroid of Claim 1 in
association with a pharmaceutical carrier or coating.

14. A pharmaceutical composition for the treatment and/or prophylaxis of disorders associated with inflammation which comprises an antiinflammatory effective amount of a compound of Claim 1 to ameliorate said disorder.

15. A process for the preparation of a compound according to Claim 1 comprising a radical fragmentation reaction of a compound of formula II:



wherein --- , R_1 , R_2 , R_4 , R_5 , R_6 are as defined in Claim 1, n is 0 and R_7 is a suitable group such as 2-thioxo-1,2-dihydropyrid-1-yloxycarbonyl, by irradiation in the presence of a compound of the general formula:



wherein R_3 is as hereinbefore defined, R_8 represents a hydrogen atom or an alkyl group containing up to about 7 carbon atoms, and m represents 0 or 2, under an inert atmosphere, n is 1 or 2 by oxidation of a compound defined in Claim 1 and if further desired when --- , forms a single bond by reduction of a compound defined in Claim 1 and if further desired when R_3 represents a halomethyl group by halogenation of a compound defined in Claim 1 and if further desired when R_4 represents an alkoxy group by alkylation of a compound defined in Claim 1.

16. A process for the preparation of a compound according to Claim 1 substantially as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/02659

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 5 C07J71/00 A61K31/56 //C07J3/00, C07J5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 5 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 004 741 (SYNTEX (U.S.A.) INC.) 17 October 1979 see the whole document ----	1, 12-15
A	GB,A,2 137 206 (GLAXO GROUP LIMITED (UNITED KINGDOM)) 3 October 1984 see the whole document -----	1, 12-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

8 March 1994

Date of mailing of the international search report

25. 03. 94

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Authorized officer

Moreno, C

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/02659

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 93/02659

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0004741	17-10-79	US-A- 4188385	12-02-80
		AT-B- 368168	27-09-82
		AU-B- 526025	16-12-82
		AU-A- 4558379	18-10-79
		CA-A- 1134345	26-10-82
		DE-A- 2912331	18-10-79
		FR-A, B 2421912	02-11-79
		GB-A, B 2018256	17-10-79
		JP-C- 1338662	29-09-86
		JP-A- 54141758	05-11-79
		JP-B- 61001038	13-01-86
		JP-C- 1374793	22-04-87
		JP-A- 60069019	19-04-85
		JP-B- 61040648	10-09-86
		SU-A- 1052161	30-10-83
		US-A- 4263289	21-04-81
GB-A-2137206	03-10-84	AT-B- 395428	28-12-92
		AT-B- 395427	28-12-92
		AT-B- 395429	28-12-92
		AU-B- 544517	06-06-85
		AU-A- 6729881	20-08-81
		BE-A- 887518	13-08-81
		CA-A- 1201114	25-02-86
		CA-C- 1205464	03-06-86
		CH-A- 644615	15-08-84
		CH-A- 651307	13-09-85
		DE-A, C 3105307	10-12-81
		DE-C- 3153379	19-11-92
		FR-A, B 2477156	04-09-81
		FR-A, B 2485542	31-12-81
		GB-A, B 2088877	16-06-82
		JP-C- 1488353	23-03-89
		JP-A- 56138200	28-10-81
		JP-B- 63037120	22-07-88
		NL-A- 8100707	16-09-81
		SE-B- 452468	30-11-87
		SE-A- 8101010	16-08-81
		US-A- 4335121	15-06-82
		US-A- 4578221	25-03-86

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 93/02659

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-2137206		US-A- 4650610	17-03-87
